Supplemental Information

Supplemental Methods

Identification of H3K27ac ChIP-seq peaks and super-enhancers

Among the possibilities of ChIP-seq data for SE identification, H3K27ac ChIP-seq data was used here, because this chromatin mark is specifically associated with active enhancers (Creyghton et al. 2010) and is available for a wide collection of samples. Sequence reads were aligned to the hg19 version of the human genome using Bowtie (Langmead et al. 2009) with parameters -k1 -m1 --best. H3K27ac enriched regions were called using MACS 1.4.2 (Zhang et al. 2008) with parameters -p 1e-9 keep-dup=auto -w -S -space=50. ROSE (https://bitbucket.org/young_computation/rose) (Lovén et al. 2013) was then used to identify SEs from the H3K27ac enriched regions as described (Hnisz et al. 2013). Briefly, H3K27ac enriched regions were considered as constituent enhancers and were stitched together when they occurred within 12.5kb. In order to distinguish the H3K27ac enhancer signal from the H3K27ac promoter signal, constituent enhancers that were fully contained within +/-1kb of a RefSeq Transcription Start Site (TSS) were disregarded for stitching. Enhancer clusters that had a H3K27ac input-subtracted signal above a computed threshold defined by ranking the H3K27ac signal at enhancer clusters were identified as SEs.

CRC Mapper

SE to gene assignment

SEs identified with ROSE (https://bitbucket.org/young_computation/rose) (Lovén et al. 2013) are assigned to the closest transcript predicted to be expressed, where distance is measured as the distance from the center of the SE to the TSS. As expression data does not exist for all cell types examined, H3K27ac read density is used to determine expression in each sample. H3K27ac read density in the region +/-1kb around the TSS is used to rank each transcript in each sample. Transcripts on this ranked list are then assigned to genes. Duplicates from the resulting ranked gene list are removed and the list is subsequently used to identify the top 2/3 of ranked genes. The read density value corresponding to the last gene in the top 2/3 is used as a threshold value that can then be applied back to identify all transcripts considered expressed. The selection of top 2/3 as a threshold is based on the observation that this threshold allows recovery of the highest percentage of expressed genes while minimizing false negatives, when the results of this method are compared to microarray and RNA-seq data in H1 ESC. This ratio of expressed genes is consistent with the ratio of genes considered expressed across cell types (Ramsköld et al. 2009).

Identification of candidate core TFs

SE-assigned transcription factors (TF) are then selected from the lists of SE-assigned genes using a list of 1253 TFs consisting of the intersection of AnimalTFDB (Zhang et al. 2012) and TcoF (Schaefer et al. 2011) lists of TFs minus CTCF, GTF2I and GTF2IRD1 that are not considered as putative core TFs (Table S2).

Motif analysis

A database of DNA sequence motifs for 695 TFs - about 60% of known TFs in vertebrates - was compiled from the TRANSFAC database of motifs (Matys et al. 2006), and from the MEME suite (January 23rd 2014 update), for the following collections: JASPAR CORE 2014 vertebrates (Mathelier et al. 2014), Jolma 2013 (Jolma et al. 2013), Homeodomains (Berger et al. 2008), mouse UniPROBE (Robasky and Bulyk 2011) and mouse and human ETS factors (Wei et al. 2010). For SE-assigned TFs with identified sequence specific binding motifs, those motifs are used to search the SE sequences assigned to the gene encoding that TF. For the motif search, the search space in SEs is restricted to extended SE constituents, as these are the regions that capture most of the TF binding in SEs (Figure 1C). SE constituent DNA sequences are extracted, extended on each side (500 bp by default) and used for motif search with FIMO (Grant et al. 2011) with p-value threshold of $1e^{-4}$ and a set of background sequences generated from the set of extended constituent sequences with fasta-get-markov.

Identification of fully interconnected auto-regulatory loops

SE-assigned TFs whose set of constituents contains at least 3 DNA sequence motif instances for their own protein products are defined as autoregulated TFs. If multiple motifs for the same TF matched an identical location, it is counted as only one motif instance. From the set of autoregulated TFs, the TFs predicted to bind to the SEs of other autoregulated TFs, using the same criteria as described above, are identified and all possible fully interconnected autoregulatory loops of TFs are then reconstructed through recursive identification. When multiple possibilities of fully interconnected autoregulatory loops are identified, the most representative fully interconnected autoregulatory loop of TFs is selected as the model of CRC. This loop is defined as the loop containing the TFs that occur the most frequently across all possible loops.

Metagenes

Genome-wide meta-representations of ChIP-seq density (in units of reads per million per base pair) were created by mapping aligned reads to SE constituents +/- 5kb using bamToGFF (https://github.com/bradnerComputation/pipeline/blob/master/bamToGFF.py) (Lin et al. 2012).

Transcription factor binding analysis

H1 hESC ChIP-seq data (Kunarso et al. 2010; Hawkins et al. 2011) were used to quantify the binding of TFs to the region +/- 1kb around cognate motifs found in SE constituents which are extended 500 bp on each side, or, as a control, in the same number of randomly selected genomic regions of the same size. The number of sequences containing motifs that overlapped with the ChIP-seq peaks identified by MACS 1.4.2 (Zhang et al. 2008) ran with parameter -p 1e-9 keep-dup=auto -w -S -space=50 were quantified. The true positive rates of TF binding was calculated by dividing the number of motif containing sequences that were bound by the TF from the ChIP-seq data analysis, over the total number of motif containing sequences.

Gene set enrichment analysis (GSEA)

GSEA (Mootha et al., 2003) analyses were performed using the tool available at http://www.broadinstitute.org/gsea/. Mean z-scores for either OCT4-GFP protein level reduction or cell nuclei count reduction (Chia et al. 2010) were used to rank the lists of all TFs and H1 hESC candidate core TFs were used as the query. The Pre-Ranked function of the GSEA software was used with 1000 iterations to generate the plots.

CRC target gene analysis

For the CRC target gene analysis, two groups of target genes were considered: expressed genes and SE-assigned genes. Expressed genes correspond to the top 2/3 genes ranked based on H3K27ac signal in the region +/-1kb around the TSS. SE-assigned genes were identified from the list of expressed genes as described above.

For H1, in each group, genes that had motif instances predicting the binding of at least 5, 6, 7, 8, 9 or 10 candidate core TFs in their combined enhancer and promoter sequences were quantified. For other cell types, genes that had motif instances predicting the binding of at least half or all candidate core TFs in their combined enhancer and promoter sequences were quantified. The region +/-1kb around the TSS and associated super or typical enhancer constituents extended 500 bp on each side were used for the motif search when all expressed genes were considered, and SE constituents extended 500 bp on each side and corresponding region +/-1kb around the TSS sequence of the SE-assigned gene were used for the motif search when SE assigned genes were considered. For the maps in Figure 3, 30 target genes selected from the CRC targets are displayed as examples. These were selected based on the number of Pubmed literature entries for each target gene associated to search terms relative to the cell type in which it was identified.

ChIP-seq tracks

Sequence reads were aligned to the hg19 version of the human genome using Bowtie (Langmead et al. 2009) with parameters -k1 -m1 --best. Wiggle tracks were created from ChIP-seq data with MACS 1.4.2 (Zhang et al. 2008) with parameters -p 1e-9 keep-dup=auto -w -S -space=50, normalized to the total number of mapped reads in the sample, and visualized in UCSC Genome Browser.

ChIP-seq

Chomatin immunoprecipitation experiments were performed in Jurkat cells (ATCC), as described (Kwiatkowski et al. 2014), with the following antibodies: anti-H3K27ac (ab4729, Abcam), anti-RUNX1 (ab23980, Abcam) and anti-GATA3 (Sc-22206X, Santa

Cruz). Purified immunoprecipitated DNA was prepared for sequencing according to a modified version of the Solexa Genomic DNA protocol, and sequenced with an Illumina HiSeq sequencer.

Microarray expression analysis

Microarray data displayed on Figure 5 were downloaded from GEO (references in Table S1). Expression values were processed using MAS5 normalization from the “affy” R package (Gautier et al. 2004). Signals for probes corresponding to the same transcript were aggregated using the standard probe assignment method (hgu133plus2cdf”). Normalized log2(expression+1) of the transcripts for the set of candidate core TFs or for all TFs considered expressed with the metric described above, are displayed for each sample. P-values were calculated using a Wilcoxon test. Affymetrix HG U133 2.0 plus microarray data performed in Jurkat cells after knock-down of either MYB, RUNX1, TAL1 and GATA3 with shRNAs were downloaded from Sanda et al., 2011. Mean of log 2 fold-change (knock-down/control) for two biological replicates using two target shRNAs per TF and two shRNAs control were extracted for either the set of Jurkat cell candidate core TFs represented on Figure 4A or for the full set of TFs considered expressed in Jurkat cells.

DNA-binding domain structure analysis

Candidate core TFs for all samples, and the compiled list of housekeeping TFs (Ramsköld et al. 2009) considered expressed in at least one of the samples, were overlapped with lists of TFs classified by DNA-binding domains (Vaquerizas et al. 2009). Percentages of DNA-binding domain containing TFs were compared between candidate core TFs and housekeeping TFs for each type of DNA-binding domain. Percentages of

TFs that were significantly different between the two groups of TFs are displayed (z-test p-value < $5e^{-2}$).

Hierarchical clustering of CRCs

A matrix of distances was calculated based on Pearson correlations between the candidate core TFs lists and plotted using R. For this analysis, we required the samples had greater than 7 TFs in their CRC for improved robustness of clustering.

Disease or trait-associated gene analysis

Disease or trait-associated gene lists were downloaded from the NHGRI catalog of published Genome-Wide Association Studies (12/5/15 update). The disease or trait-associated genes overlapping with the list of core or non-core TFs were quantified. For each disease or trait, the proportion of the overlapping candidate core TFs and non-core TFs were compared with a z-test. The disease or traits for which z-test p-value < $5e^{-2}$, are displayed and -log(p-values) values are plotted on the radar plot.

Comparison of networks

For the set of TFs in the CRC that are represented in the transcriptional network for a corresponding cell type (Neph et al. 2012), we extracted the set of TF-TF interactions predicted in the CRC, where interactions are defined as predicted TF binding to the regulatory sequences of another TF. We then computed the number of TF-TF interactions predicted in the CRC which are also predicted in the transcriptional network for a corresponding cell type (Neph et al. 2012). As a control, we did the same analysis, for each sample, using a set of the same number of randomly selected TFs that are not part of the CRC, but that are represented in the network for a corresponding cell type

(Neph et al. 2012). We then compared the percentage of overlap obtained for the CRC set of interactions, with the percentage of overlap obtained for the control set of interactions, with a z-test.

Supplemental Figure Legends

Figure S1. Example of CRC model selection out of multiple CRCs. The TF content of each possible Interconnected autoregulatory loop (IAL) in H1 hESC is plotted in each column. The TFs were ranked vertically by decreasing fraction of their occurrences across all the possible IALs. The loops are ranked from left to right by average fraction of TF occurrence in the loops. The CRC model corresponds to the leftmost loop.

Figure S2. Effect of H1 hES candidate core TF depletion on pluripotency and proliferation. (A) Rank of each candidate core TF among all TFs for mean of z-score for OCT4-GFP fluorescence reduction and nuclei number reduction from 2 experimental replicates, from siRNA screen data in H1 hES (Chia et al. 2010). (B) Gene-Set Enrichment Analysis (GSEA) for the candidate core TFs compared to all TFs for *POU5F1/OCT4-GFP* expression values. (C) GSEA analysis for the candidate core TFs compared to all TFs for nuclei number values.

Figure S3. ChIP-seq data for TFs in the CRC support the predicted binding interactions for 3 additional cell types. ChIP-seq data showing binding of the TFs to the SEs of the candidate core TF for (A) CD20+ B-cell, (B) HCT-116 colon cancer cell line, and (C) MCF-7 breast cancer cell line. Red lines on top of the tracks depict SE genomic locations.

Figure S4. TF associated with the indicated diseases through GWAS in the CD20+ B-cell CRC model. Genes associated with a given disease through GWAS are colored according to the key. SEs that overlap SNPs associated with a given disease or trait through GWAS are colored according to the key.

Figure S1

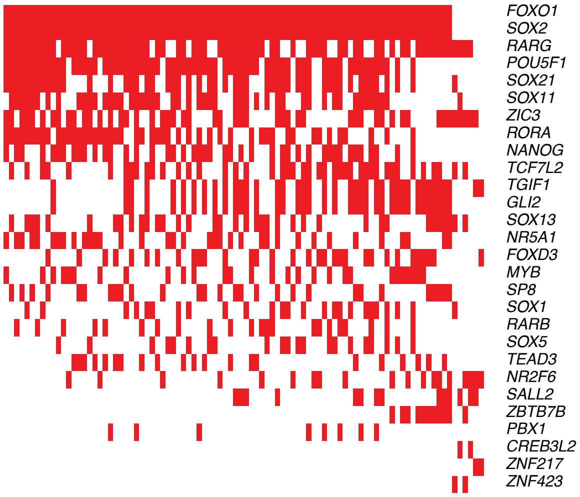

FOXO1
SOX2
RARG
POU5F1
SOX21
SOX11
ZIC3
RORA
NANOG
TCF7L2
TGIF1
GLI2
SOX13
NR5A1
FOXD3
MYB
SP8
SOX1
RARB
SOX5
TEAD3
NR2F6
SALL2
ZBTB7B
PBX1
CREB3L2
ZNF217
ZNF423

Figure S2

A

OCT4-GFP fluorescence changes Rank for mean of z-scores (% of TFs)		Nuclei number changes Rank for mean of z-score (% of TFs)	
POU5F1	0	NR5A1	4
ZIC3	5	POU5F1	9
NANOG	5	NANOG	11
RARG	27	SOX21	19
SOX2	34	ZIC3	22
MYB	39	SOX2	24
NR5A1	64	RARG	31
FOXO1	83	RORA	33
RORA	86	FOXO1	38
SOX21	89	MYB	66

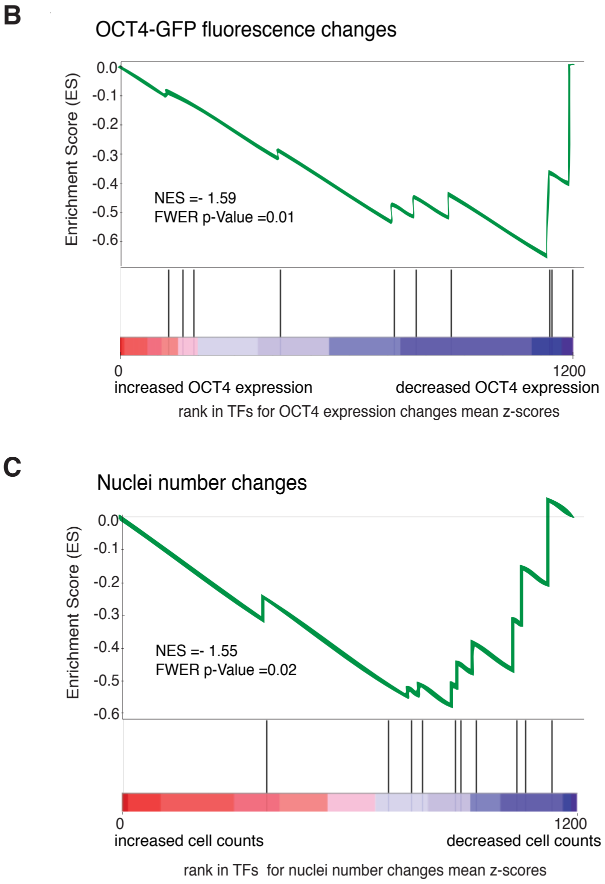


Figure S3

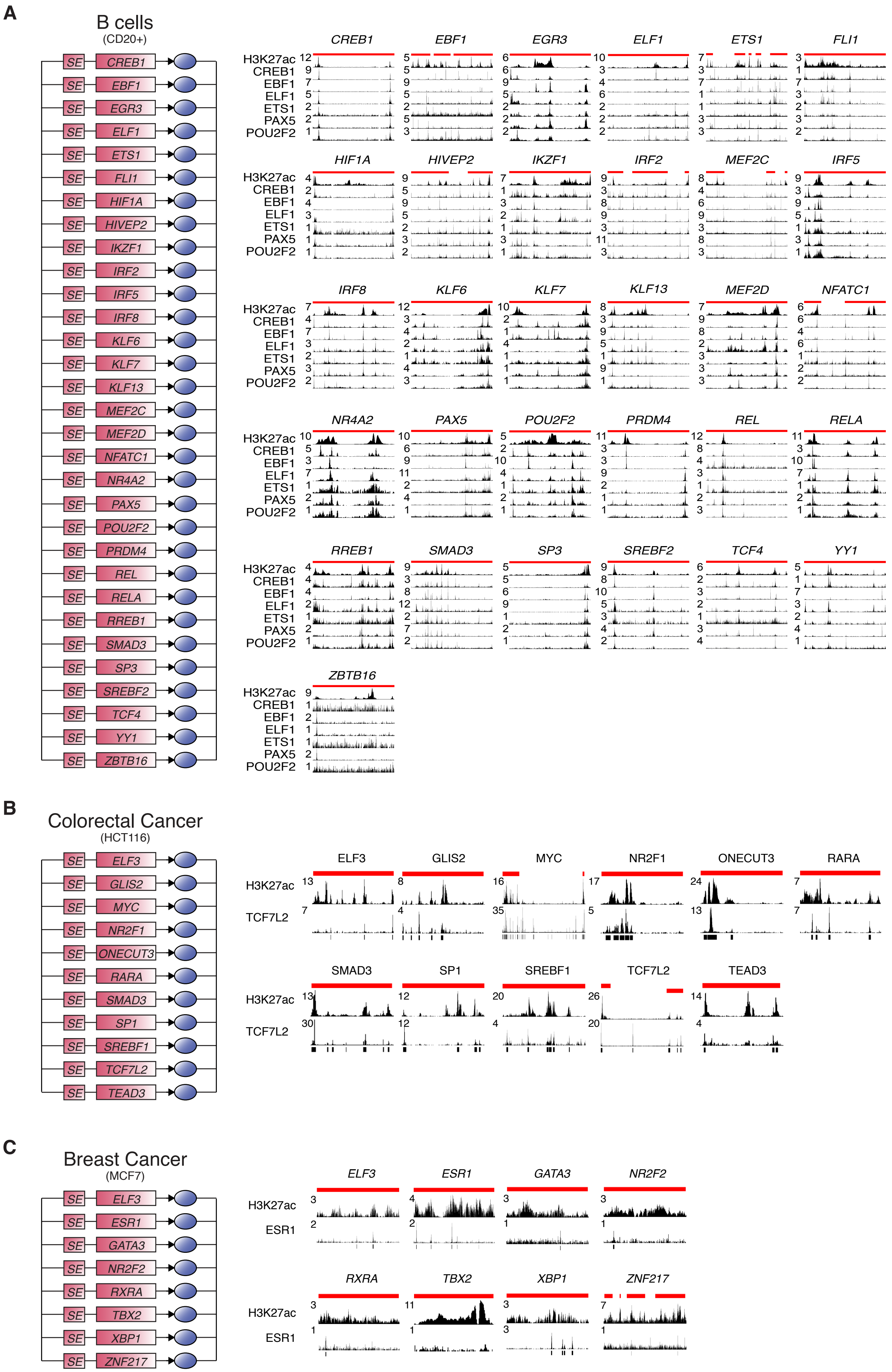
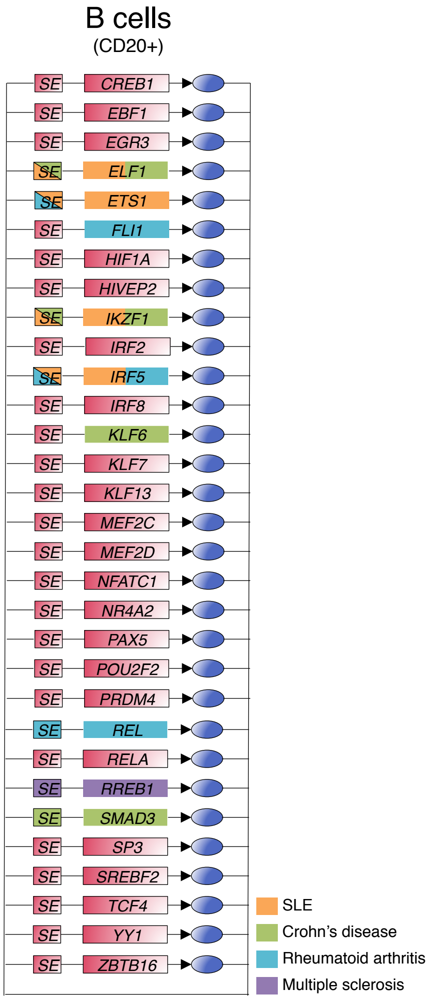

A
B cells
(CD20+)
SE CREB1
SE EBF1
SE EGR3
SE ELF1
SE ETS1
SE FLI1
SE HIF1A
SE HIVEP2
SE IKZF1
SE IRF2
SE IRF5
SE IRF8
SE KLF6
SE KLF7
SE KLF13
SE MEF2C
SE MEF2D
SE NFATC1
SE NR4A2
SE PAX5
SE POU2F2
SE PRDM4
SE REL
SE RELA
SE RREB1
SE SMAD3
SE SP3
SE SREBF2
SE TCF4
SE YY1
SE ZBTB16
H3K27ac
CREB1
EBF1
ELF1
ETS1
PAX5
POU2F2
CREB1 12 9 7 5 2 2 1
EBF1 5 5 5 5 2 5 3
EGR3 6 6 9 5 2 2 2
ELF1 10 3 4 6 2 2 2
ETS1 7 3 7 1 1 3 3
FLI1 3 1 7 3 2 3 2
HIF1A 4 2 4 3 1 1 1
HIVEP2 9 5 9 5 2 3 2
IKZF1 7 1 3 2 1 3 1
IRF2 9 3 8 9 3 11 3
MEF2C 8 4 6 9 3 8 3
IRF5 9 3 9 5 1 3 1
IRF8 7 4 7 3 2 3 2
KLF6 12 3 4 2 1 4 3
KLF7 10 2 1 4 1 1 1
KLF13 8 3 9 5 1 9 1
MEF2D 7 9 8 2 3 3 3
NFATC1 6 6 4 6 1 2 2
NR4A2 10 5 3 7 1 2 1
PAX5 10 6 9 11 2 4 1
POU2F2 5 2 10 4 1 2 1
PRDM4 11 3 3 9 2 1 1
REL 12 8 4 3 1 2 3
RELA 11 3 10 7 1 2 1
RREB1 4 4 4 2 1 2 1
SMAD3 9 3 8 12 2 7 2
SP3 5 5 6 9 1 2 1
SREBF2 9 8 10 5 3 4 2
TCF4 6 2 3 2 1 3 4
YY1 5 1 7 3 2 4 1
ZBTB16 9 1 2 1 1 2 1
B
Colorectal Cancer
(HCT116)
SE ELF3
SE GLIS2
SE MYC
SE NR2F1
SE ONECUT3
SE RARA
SE SMAD3
SE SP1
SE SREBF1
SE TCF7L2
SE TEAD3
H3K27ac
TCF7L2
ELF3 13 7
GLIS2 8 4
MYC 16 35
NR2F1 17 5
ONECUT3 24 13
RARA 7 7
SMAD3 13 30
SP1 12 12
SREBF1 20 4
TCF7L2 26 20
TEAD3 14 4
C
Breast Cancer
(MCF7)
SE ELF3
SE ESR1
SE GATA3
SE NR2F2
SE RXRA
SE TBX2
SE XBP1
SE ZNF217
H3K27ac
ESR1
ELF3 3 2
ESR1 4 2
GATA3 3 1
NR2F2 3 1
RXRA 3 1
TBX2 11 1
XBP1 3 3
ZNF217 7 1

Figure S4


B cells
(CD20+)
SE
CREB1
EBF1
EGR3
ELF1
ETS1
FLI1
HIF1A
HIVEP2
IKZF1
IRF2
IRF5
IRF8
KLF6
KLF7
KLF13
MEF2C
MEF2D
NFATC1
NR4A2
PAX5
POU2F2
PRDM4
REL
RELA
RREB1
SMAD3
SP3
SREBF2
TCF4
YY1
ZBTB16
SLE
Crohn's disease
Rheumatoid arthritis
Multiple sclerosis

Supplemental Tables

Table S1. List of samples and GEO accession nimbers for the ChIP-seq and expression datasets.

Table S2. List of TFs and associated motifs.

Table S3. Lists of SE-assigned TFs, autoregulated TFs, CRC models and extended regulatory circuitry for 84 samples.

Table S4: List of H1 CRC SE-assigned target genes whose expression is modified after POU5F1/OCT4 knock-down in H1 hESCs.

Table S5. H1 CRC SE-assigned target gene examples.

Table S6. Results for MIR371 target genes for TargetScan, miRDB and PITA miRNA target predictor software.

Table S7. Functions of the candidate core TFs for five well-studied cell types.

Table S8. Comparison of CRC models with Neph et al. networks.

Table S5. H1 CRC SE-assigned target gene examples

Targets	Role in ESC biology	References
Transcription factors		
GLI2	Involved in mESC self-renewal.	Li et al., 2013
PBX1	Required for the maintenance of hESC identity.	Chan et al., 2009
PRDM14	Required for the maintenance of hESC identity.	Chia et al., 2010
SALL4	Required for the maintenance of mESC identity.	Zhang et al., 2006
ZNF281/ZFP281	Required for proper differentiation in mESCs.	Seo et al., 2013; Wang et al., 2008; Fidalgo et al., 2011; Fidalgo et al., 2012
ZSCAN10/ZFP206	Required to maintain pluripotency and for differentiation in mESC.	Yu et al., 2009
miRNA machinery		
LIN28B	RNA binding protein. Represses let-7 miRNA expression, tightly regulated during differentiation. Can be used to reprogram fibroblasts into iPSCs. May directly promote the translation of various cell cycle regulators.	Viswanathan et al., 2010; Hagan et al., 2009; Melton et al., 2010; Yu and Thomson et al., 2007; Xu et al., 2009
MIR371	Human homolog of murine mir290, the most abundant miRNA in mESCs, essential for their survival. Functional assays in human cancer cells support reciprocal expression regulation of MIR371 and SOX2, which is a highly predicted target of miR-371.	Medeiros et al., 2011; Calabrese et al., 2007; Sinkkonen et al., 2008; Marson et al., 2008
TRIM71/mLin41	miRISC-interacting protein. Promotes ESC self-renewal by facilitating the G1-S transition. Target of let-7 mi-RNA.	Chang et al., 2012
chromatin regulators		
DNMT3B	DNA methyltransferase required at the ESC differentiation step to silence *POU5F1* and *NANOG* gene expression.	Jackson et al., 2004; Feldman et al., 2006
DPPA4	Chromatin binding protein involved in ESC self-renewal.	Ivanova et al., 2010
JARID2	Polycom (PcG) protein. Helps silence genes encoding key regulators of development, yet allowing them to remain in a “poised” state for activation.	Bernstein et al., 2006; Lee et al., 2006, Young et al. 2011; Das et al., 2014
KDM2B	H3K36me2 demethylase. Promotes recruitment of the PcG proteins to establish a poised chromatin state on genes encoding key regulators of development.	He et al., 2013
SETDB1	H3K9me3 methylase. Promotes recruitment of the PcG proteins to establish a poised chromatin state on genes encoding key regulators of development.	Bilodeau et al., 2009; Yeap et al., 2009; Yuan et al., 2009; Kagey et al., 2010
long ncRNA		
MALAT1	Promotes cellular proliferation by modulating the expression and pre-mRNA processing of cell cycle-regulated transcription factors in various cancer cells.	Tripathi et al., 2010; Tripathi et al., 2013; Li et al., 2009; Gutschner et al., 2012

Table S7. Functions of the candidate core TFs for five well-studied cell types

TF	Role in cell identity	References
	B-cell (CD20+)	
CREB1	Involved in B cell activation and proliferation via the B cell receptor signaling pathway	Yasuda et al., 2008; Blois et al., 2004
EBF1	Required for normal B cell differentiation	Lin and Grosschedl, 1995
EGR3	Required with EGR2 for antigen receptor-induced proliferation	Li et al., 2012
ELF1	Regulates production of diverse lymphocyte repertoire	Grant et al., 1995; Akbarali et al., 1996; Ernst et al., 1996
ETS1	Required for normal B and T cell differentiation	Bories et al., 1995; Eyquem et al., 2004a; Eyquem et al., 2004b; Andersson et al., 1999
FLI1	Required for expression of B cell receptor	Maier et al., 2003; Bradshaw et al., 2008; Zhang et al., 2008
HIF1A	Required for normal B cell differentiation	Kojima et al., 2002
HIVEP2	Involved in regulation of MHC class I genes	van't Veer et al., 1992
IKZF1	Involved in B and T cell differentiation	Georgopoulos et al., 1994; Wang et al., 1996
IRF2	Regulates proliferation and antibody production	Matsuyama et al., 1993; Minamino et al., 2012
IRF5	Required for normal B cell differentiation	Lien et al., 2010
IRF8	Required for normal B cell differentiation	Lu et al., 2003; Ma et al., 2006; Wang et al., 2008
KLF13	Required for normal B cell differentiation	Outram et al., 2008; Gordon et al., 2008
KLF6		
KLF7		
MEF2C	Regulates proliferation and antibody production	Rao et al., 1998; Swanson et al., 1998; Wilker et al., 2008; Khiem et al., 2008; Gekas et al., 2009
MEF2D		
NFATC1	Required for normal B cell differentiation	Peng et al., 2001; Berland and Wortis, 2003; Bhattacharyya et al., 2011
NR4A2	Regulates immune homeostasis	Sekiya et al., 2011; Sekiya et al., 2013
PAX5	Required for normal B cell differentiation	Urbanek et al., 1994; Nutt et al., 1999
POU2F2	Required for normal B cell differentiation	Corcoran et al., 1993
PRDM4		
REL	Regulates proliferation and survival in response to activation	Kontgen et al., 1995; Harling-McNabb et al., 1999; Tumang et al., 2002)
RELA	Required for proliferation of developing B cells	Prendes et al., 2003
RREB1		
SMAD3	Regulates antibody production	Stavnezer and Kang, 2009; Coffman et al., 1989; Sonoda et al. 1989
SP3	Required for normal hematopoiesis	van Loo et al., 2003
SREBF2		
TCF4/E2-2	Required for normal B cell differentiation	Zhuang et al., 1996
YY1	Required for normal antibody production	Liu et al., 2007; Green et al., 2011; Pan et al., 2013
ZBTB16	Required for normal hematopoiesis	Savage et al., 2008; Kovalovsky et al., 2008; Raberger et al., 2008
	Heart (Left Ventricule)	
ETS1	Required for normal heart development	Gao et al., 2010; Ye et al., 2010; Lie-

		Venema et al., 2003
FOXK1	Regulates cardiac and skeletal myogenic progenitors	Shi et al., 2012
FOXO3	Regulates cardiac hypertrophy	Skurk et al., 2005; Sengupta et al., 2009; Sengupta et al., 2011; Schips et al., 2011
IRF1	Regulates cardiac hypertrophy	Jiang et al., 2014
KLF13	Required for normal heart development	Lavallee et al., 2006
KLF15	Pleiotropic regulator of cardiac function and metabolism	Fisch et al., 2007; Noack et al., 2012; Prosdocimo et al., 2014; Jeyaraj et al., 2012; Leenders et al., 2010;
KLF7		
MEIS1	Required for normal heart development	Stankunas et al., 2008; Mahmoud et al., 2013
NKX2-5	Required for normal heart development	Lyons et al., 1995; Komuro and Izumo, 1993; Lints et al., 1993
NR2F2	Required for normal heart development	Pereira et al., 1999; Al Turki et al., 2014
NR4A1	Regulates cardiac hypertrophy and apoptosis	Wang et al., 2009; Cheng et al., 2011; Wang et al., 2013
PBX1	Required for normal heart development	Stankunas et al., 2008; Chang et al., 2008; Arrington et al., 2012
RARA	Contributes to normal heart development	Kastner et al., 1997; Lee et al., 1997; Luo et al., 1996; Mendelsohn et al., 1994
RARB	Contributes to normal heart development	Luo et al., 1996
RREB1		
RXRA	Contributes to normal heart development	Kastner et al., 1997; Sucov et al., 1994; Gruber et al., 1996; Kastner et al., 1994
SMAD3	Regulates antibody production	Stavnezer and Kang, 2009; Coffman et al., 1989; Sonoda et al. 1989
SOX18	Required for normal heart development	Zhang et al., 2005; Sakamoto et al., 2007;
TBX20	Required for normal heart development	Stennard et al., 2003; Reim et al., 2005; Singh et al., 2005; Stennard et al., 2005; Takeuchi et al., 2005; Cai et al., 2005; Qian et al., 2005; Miskolczi-McCallum et al., 2005; Brown et al., 2005
TBX5	Required for normal heart development	Li et al., 1997; Basson et al., 1997; Ieda et al., 2010; Nam et al., 2014; Song et al., 2012
TEF	Contributes to normal heart function	Wang et al., 2010
THRA	Contributes to normal heart function	Forrest and Vennstrom, 2000; Fraichard et al., 1997; Gauthier et al., 2001; Gauthier et al., 1999; Kahaly et al., 2002
	Pancreas	
BHLHE41		
HES1	Required for normal pancreas development	Jensen et al., 2000; Kageyama et al., 2000
KLF13		
NR2F6		
NR4A1	Required for beta-cell proliferation and insulin secretion	Briand et al., 2012; Tessem et al., 2014
PDX1	Required for normal pancreas development	Jonsson et al., 1994; Horb et al., 2003; Zhou et al., 2008
PKNOX2		

RARA	Required for normal pancreas development	Chen et al., 2004; Ostrom et al., 2008; Matthews et al., 2004; Chertow et al., 1987
RREB1		
RXRA	Required for normal pancreas development	Chen et al., 2004; Ostrom et al., 2008; Matthews et al., 2004; Chertow et al., 1987
SMAD3	Required for normal pancreas development	Wandzioch and Zaret, 2009; Lin et al., 2009; El-Gohary et al., 2013
SOX13		
TEF		
	Adipocytes (Adipose Nuclei)	
CREB3L2		
EBF1	Required for normal adipocyte differentiation	Akerblad et al., 2002
ELK3		
ETS1		
FLI1		
FOXO1	Regulates normal adipocyte differentiation	Nakae et al., 2003
HBP1		
IRF1		
KLF11	Contributes to regulation of lipid metabolism	Zhang et al., 2013; Yamamoto et al., 2010
MEF2D	Contributes to regulation of glucose metabolism	Sparling et al., 2007
NFIA	Required for normal adipocyte differentiation	Waki et al., 2011
NR2F2	Regulates normal adipocyte differentiation	Xu et al., 2008;
NR3C1	Regulates normal adipocyte differentiation and lipid metabolism	Chapman et al., 1985; Hauner et al., 1987
PBX1	Regulates normal adipocyte differentiation	Monteiro et al., 2011
PPARG	Required for normal adipocyte differentiation	Tontonoz et al., 1994
RARA	Regulates normal adipocyte differentiation	Murray and Russell, 1980; Kuri-Harcuch, 1982; Castro-Munozledo et al., 1987; Stone and Bernlohr, 1990; Kamei et al., 1994
RFX2		
RREB1		
RUNX1		
RXRA	Regulates normal adipocyte differentiation	Murray and Russell, 1980; Kuri-Harcuch, 1982; Castro-Munozledo et al., 1987; Stone and Bernlohr, 1990; Kamei et al., 1994
SMAD3	Regulates normal adipocyte differentiation	Choy et al., 2000; Choy and Derynck, 2003; Epperly et al., 2005
STAT3	Required for normal adipocyte differentiation	Wang et al., 2009; Zhang et al. 2011; Derecka et al., 2012
STAT5B	Regulates normal adipocyte differentiation	Nanbu-Wakao et al., 2002; Floyd and Stephens, 2003
TCF7L2	Regulates normal adipocyte differentiation	Ross et al., 2000
ZNF217		
	Brain (Hippocampus Middle)	
ATF1		
ERF	Required for normal neuronal differentiation	Janesick et al., 2013
IRF1	Regulates response to cerebral inflammation and damage	Jarosinski and Massa, 2002; Iadecola et al., 1999; Park et al., 1998
IRF2	Regulates response to cerebral inflammation and damage	Park et al., 1998
KLF13		

MEF2D	Required for normal neuronal differentiation; regulates neuron plasticity; neuronal survival factor	Flavell et al., 2006; Smith et al., 2006; Salma and McDermott, 2012; Chen et al., 2012; Gong et al., 2003
NKX6-2	Neuronal survival factor; required for normal CNS development	Hashimoto et al., 2004; Southwood et al., 2004; Ma et al., 2013; Dichman and Harland, 2011;
NR2F2	Required for normal CNS development	Kim et al., 2009; Tang et al., 2012; Naka et al., 2008; Kanatani et al., 2008; Tripodi et al., 2004
NR4A1	Regulates synaptic function	Bridi and Abel, 2013; McNulty et al., 2012
POU3F3	Contributes to normal CNS development	Dominguez et al., 2013; Sugitani et al., 2002
RARA	Regulates synaptic function; contributes to normal neuronal differentiation; contributes to normal memory function	Nomoto et al., 2012; Chen and Napoli, 2008; Aoto et al., 2008
RXRA	Regulates synaptic function; contributes to normal neuronal differentiation; contributes to normal memory function	Nomoto et al., 2012; Chen and Napoli, 2008; Aoto et al., 2008
SOX13	Contributes to normal neuronal differentiation	Pla et al., 2008
SOX2	Required for normal neuronal differentiation; mutations associated with hippocampal malformations; required for maintenance of neural progenitors	Ferri et al., 2004; Graham et al., 2003; Sisodiya et al., 2006; ; Lujan et al., 2012
SOX8	Required for normal oligodendrocyte differentiation	Stolt et al., 2004; Stolt et al., 2005
SREBF1	Regulates fatty acid homeostasis during neuronal differentiation	Tabernero et al., 2001; Pai et al., 1998; Velasco et al., 2003
TCF4	Required for normal neuronal differentiation; mutations associated with neurological disorders	Flora et al., 2007; Fu et al., 2009; Brockschmidt et al., 2007; Zweier et al., 2007; Amiel et al., 2007; Brzozka et al., 2010
TEF	Component of circadian clock; mutations associated with neurological disorders	Gachon et al., 2004; Hua et al., 2012a; Hua et al., 2012b
ZBTB16	Required for normal neuronal differentiation	Gaber et al. 2013; Sobieszczuk et al., 2010

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